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## THE NEED FOR XENOTRANSPLANTATION AS A SOURCE OF ORGANS AND CELLS FOR CLINICAL TRANSPLANTATION

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### Abstract

The limited availability of deceased human organs and cells for the purposes of clinical transplantation remains critical worldwide. Despite the increasing utilization of ‘high-risk’, ‘marginal’, or ‘extended criteria’ deceased donors, in the U.S. each day 30 patients either die or are removed from the waiting list because they become too sick to undergo organ transplantation. In certain other countries, where there is cultural resistance to deceased donation, e.g., Japan, the increased utilization of living donors, e.g., of a single kidney or partial liver, only very partially addresses the organ shortage. For transplants of tissues and cells, e.g., pancreatic islet transplantation for patients with diabetes, and corneal transplantation for patients with corneal blindness (whose numbers worldwide are potentially in the millions), allotransplantation will never prove a sufficient source. There is an urgent need for an alternative source of organs and cells. The pig could prove to be a satisfactory source, and clinical xenotransplantation using pig organs or cells, particularly with the advantages provided by genetic engineering to provide resistance to the human immune response, may resolve the organ shortage. The physiologic compatibilities and incompatibilities of the pig and the human are briefly reviewed.

### Keywords

cell transplantation; pig; organ shortage; organ transplantation; xenotransplantation

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTION

BE, DKCC, AJT – all participated in review of the literature, writing of the manuscript, and final approval of the manuscript

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## INTRODUCTION

Organ transplantation is an established therapy for a variety of end-stage organ diseases. Today, improved surgical techniques and our understanding of the immune system have increased survival of patients with organ allografts. In the U.S., more than 617,000 solid organ transplants, including kidney, liver, pancreas, intestine, heart, and lung, have been performed since 1988 [1]. Worldwide, the numbers are probably at least double the US figure. Although most attention has been directed towards transplantation of solid organs, corneal transplantation, bone marrow transplantation, isolation and transplantation of cells and tissues with specific differentiated functions (e.g., pancreatic islets) represent important additional clinical therapies.

The major current problem in organ transplantation is the gap between the number of available transplantable organs that become available each year and the number of patients waiting for an organ graft (Figure 1) [2]. In the U.S., due to the lack of sufficient transplantable organs, each day 30 people either die while waiting for a transplant or are removed from the waiting list because they become too sick to undergo a transplant [2].

Significant changes in attitude and law towards organ donation would make increased numbers of organs available, but the supply would remain inadequate. In 1991, there were 6,953 deceased human donors, enabling 15,756 organ transplants to be carried out, and 23,198 patients on the waiting list. A decade later, in 2001, although there were 12,702 donors (an 83% increase), enabling 24,239 transplants to be performed (a 54% increase), the waiting list had expanded to 79,524 patients (a 243% increase). The significant increase in donation was partially the result of the National Organ Transplant Act signed by President Ronald Regan in October 1984 [3]. This law was signed 30 years ago and was aimed to establish the legal framework for the procurement, donation, and transplantation of organs. It was hoped that the law would end the organ shortage. However, the 85% increase in donation rate was offset by a 243% increase in patients on the waiting list, which resulted from the documented better outcomes after organ transplantation compared to alternative therapies.

In the 21<sup>st</sup> century, the increase in the number of deceased donors and organ transplants has not been as significant as before. In 2004, there were 14,154 donors (11% increase from 2001), 27,040 transplants (11% increase from 2001), and 87,146 patients on the waiting list (10% increase from 2001). In the last decade (2004–2013), the increases in the numbers of donors and transplants have been minimal or small (a 0.7% increase in donors, and a 7% increase in transplants). The increased number of transplants despite virtually no increase in the number of donors is associated with (i) the liberalization of acceptance criteria of ‘high-risk’, ‘marginal’, or ‘extended criteria’ donors, and (ii) the utilization of more organs from a single donor. However, during this period, there was a 39% increase in the number of patients on the waiting list, which rose to approximately 122,000 [1,2].

The improved medical care that results in the substantial increase in patients on the waiting list is a great economic burden to the US (and to other Western countries). For example, Medicare covers the costs of care for end-stage renal disease regardless of patient age. In

2011, over 500,000 people took advantage of this benefit at a cost of over US\$34 billion, which is more than 6% of Medicare's entire budget [4]. If we add the cost of care for other end-stage organ failures, \$US400 billion is spent each year, which is equivalent to almost 60% of Medicare's budget.

According to the World Health Organization, >114,000 organ transplants are carried out annually in the world [5,6], which is <10% of global needs. The most frequently transplanted organ is the kidney, which accounts for 68% of the total organ transplants. Deceased donors account for 60–65% of all transplanted kidneys in many countries. However, this rate drops to 5–17% in regions where deceased donation is uncommon for religious or cultural reasons, such as the Middle East, Indonesia, and Japan. Although the best donation rate in deceased organs (both donation after brain and cardiac deaths) is achieved in Spain (36 per million population), organ shortage remains a major big problem in Europe [6]. Unfortunately, organ donation does not significantly increase in countries with a highly-educated population. In several developed countries, organ donation per million remains disappointingly low. For example, in Japan the organ donation rate is only 4 per million. In most Western countries, it is less than optimal, e.g., in Switzerland it is 12 per million, in Canada 15, in the UK 18, and in the US 24 [7].

The donation rate is critical where the needs are greatest, such as in India (1 donor per million population) and in China (0.5 donor per million population). In China, about 300,000 patients would benefit from organ transplants annually, but only about 10,000 transplants are currently carried out [8], which makes the ratio of supply to demand for organ transplants 1:304. However, statistics from the World Health Organization show that the mean ratio of organ supply to demand worldwide is 1:25 [9].

In addition, in the US, approximately 30 million patients suffer from diabetes (Types 1 and 2), and millions more from other disorders that might be potentially amenable to treatment by cell or tissue transplantation, e.g., neurodegenerative diseases. Worldwide, the impact is even greater since an estimated 340 million people are afflicted by diabetes alone [10].

Although corneal allotransplantation is readily available in the U.S. and in certain other countries of the developed world, the worldwide need for human donor corneas far exceeds supply, especially in China, India, Korea, and Japan, where cultural and religious concerns make it difficult to obtain corneas from human cadavers [11]. For example, in China, there are an estimated 4 million people in need of corneal transplantation.

The increased utilization of living organ donors has helped, particularly in countries where there is cultural resistance to deceased organ donation, e.g., Japan, but this has had relatively little impact on the overall need for organs; some organs, of course, e.g., the heart, clearly can only be obtained from deceased donors. Moreover, the shortage of deceased donors and the relative success of organ transplants from living donors resulted in the problem of organ trafficking, which remains a problem in some parts of the world. It is estimated that 5–10% of kidney transplants worldwide result from commercial transactions between a potential recipient and a paid living donor [12]. The organ shortage has also led to the use of organs

from executed prisoners in some countries [13]; whether truly informed consent has been obtained remains controversial.

It is clear that the current law, rate of organ donation (both deceased and living), and liberalized acceptance criteria (i.e., use of high-risk donors, marginal, or extended criteria donors) are not enough, and will never be enough to overcome the problem of organ shortage.

## POTENTIAL OF XENOTRANSPLANTATION

Xenotransplantation, i.e., cross-species transplantation, using pig organs, could resolve the shortage of suitable donor organs [14,15]. If pig organs or cells could be transplanted successfully into human patients, the advantages would be numerous (Table 1).

Ethically, pigs represent an acceptable choice as an alternative source of organs for humans [14,16]. An estimated 100 million pigs are slaughtered in the US each year as sources of meat, and 600 million are killed in China to provide heparin. Immunologically, however, the pig is less desirable than the nonhuman primate as a source of organs and cells because of the genetic distance between pigs and humans. The clinical application of xenotransplantation has been held back because it has proved difficult to prevent immune injury of pig grafts, a subject that is discussed by several authors elsewhere in this issue. Most major advances that have been made in this field have resulted from the introduction of genetically-engineered pigs or novel immunosuppressive agents. The current reported survival periods of various pig organ and cell transplants in nonhuman primates are indicated in Figure 2.

Even if the remaining immunological and biological barriers can be resolved, which seems increasingly likely, the question needs to be asked as to whether pig organs will function adequately when transplanted to a human host. Ibrahim et al [17] have discussed selected physiological compatibilities and incompatibilities between humans and pigs, and these will be briefly reviewed here.

### Heart

Anatomically, the pig heart is similar, although not identical, to the human heart. Physiologically, cardiac output and stroke volume, which are major indicators of cardiac function, have been reported to be comparable in pig and human [17]. Mean arterial pressure, heart rate, and myocardial blood flow are also nearly identical in the two species. The upright posture in humans, in contrast to pigs, does have an evolutionary impact on the structure of heart valves but this issue has been proved to be an insignificant problem in pig-to-nonhuman primate studies [18,19]. The different action potential of cardiomyocytes related to morphological differences in the atrioventricular node between species might potentially result in increased arrhythmogenicity of a pig heart transplanted into a human, but observations of pig hearts functioning in nonhuman primates for prolonged periods have not indicated that this will be a problem [17,18].

## Kidney

The kidney has a major role in maintaining homeostasis, excretion of metabolites, electrolyte balance, regulating body fluid and osmolarity. Pig kidney anatomy is remarkably similar to the human kidney. The maximum concentrating ability (1080 mOsm/L) and glomerular filtration rate (126–175 ml/h) of porcine kidneys are similar to those of human kidneys [17]. Kidney function in healthy humans and  $\alpha$ 1,3-galactosyltransferase gene-knockout (GTKO) pigs is compared in Table 2. Although serum potassium is slightly higher in pigs, the other serum electrolytes, creatinine, and urea nitrogen are similar between pig and human. Proteinuria has been identified as an important complication after pig kidney xenotransplantation [20–22], but recent evidence suggests it is associated with continuing immune activation of the kidney [Iwase H, et al, personal communication]. Pig kidneys have been demonstrated to adequately maintain homeostasis, electrolyte balance, and osmolarity in nonhuman primates [20,23].

## Liver

Pig liver anatomy is slightly different from human liver anatomy. The pig liver has 3 lobes - the right lateral, the median, and the left lateral lobes. The median lobe is further subdivided by a deep umbilical fissure, which extends almost to the hilum [24]. The inferior vena cava is intraparenchymal and runs within the caudate lobe.

The liver has diverse functions, ranging from the synthesis of many vital proteins, coagulation factors, and biochemical molecules to detoxification of harmful substances. Table 3 compares liver function in healthy humans and pigs. Although there are several similarities in hepatic function, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and gamma glutamyltransferase (GGT) are higher in pigs [25,26]. It is more important, however, to demonstrate that similarities should not be limited to the measurement of enzyme levels, but should compare function as well. Studies by Ekser et al [27], and Kim et al [28] suggest that a pig liver may function adequately in a nonhuman primate, producing coagulation factors that maintain a normal coagulation profile.

## Lung

Although experimental experience with the xenotransplantation of pig lungs is limited, in part relating to the severe vasoconstriction that occurs in the newly-transplanted lungs, the pig lung has been demonstrated to provide adequate oxygenation and carbon dioxide exchange in nonhuman primates [29]. The upright posture of humans may also have an impact of physiological function of the pig lung after xenotransplantation. However, due to the limited survival achieved with pig lungs in nonhuman primates (<5 days), no definite conclusions can be made.

## Pancreatic Islets

Porcine insulin differs from human insulin by only one amino acid, and is functionally comparable to human insulin. Porcine insulin was used for decades to treat patients with diabetes. There is good evidence, therefore, that well-functioning pig islets will be able to maintain normoglycemia in diabetic patients [30].

## Neuronal cells

Although there is only one significant study, the evidence is that porcine dopamine-producing cells can reverse the clinical features of a Parkinson-like disease in monkeys [31].

## Corneas

There are similarities between pig and human corneas (Table 4).

## CONCLUSIONS

Organ shortage is an undeniable problem in organ transplantation and is increasingly problematic. Even if we are able to increase donation rates significantly, allotransplantation will never be able to provide sufficient islets for all diabetic patients. As discussed elsewhere in this issue, approaches such as stem cell therapy or bioengineered devices are not sufficiently successful yet to consider as an alternative to allotransplantation. Xenotransplantation is much closer to meaningful clinical trials, and these could be initiated either through cellular xenotransplantation [15,30,31] or as a ‘bridge’ to liver [32] or heart [33] allotransplantation.

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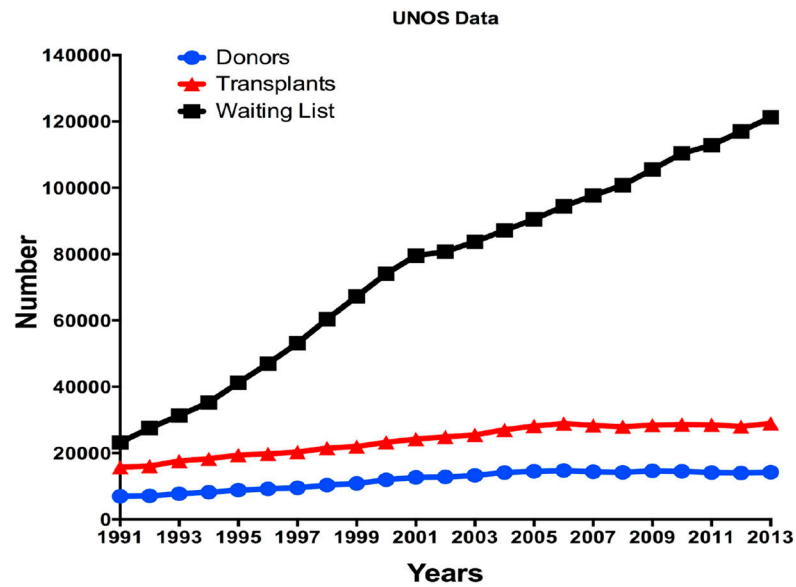
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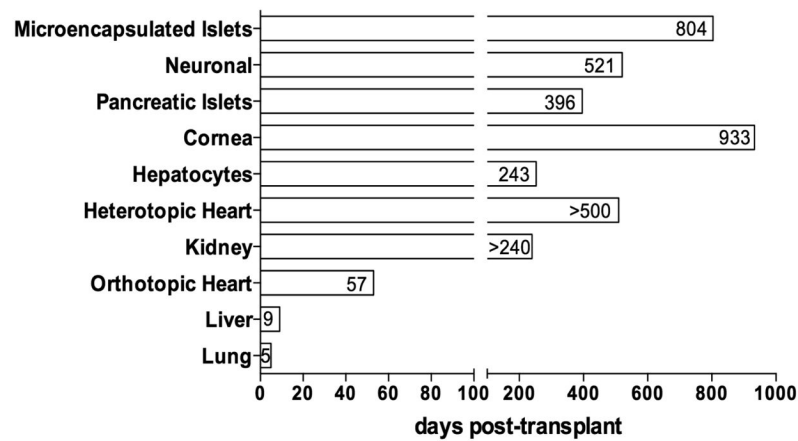
**HIGHLIGHTS**

- In the US each day, 30 dead or sick patients are removed from the waiting list
- The available donors are not enough to overcome the global organ shortage
- Pigs represent an alternative source of organs for humans
- The pig could be a satisfactory source of organs for clinical transplantation
- New technologies are facilitating the genetic engineering of pigs



**Figure 1. Trends in the numbers of organ donors (blue), organ transplants (red), and patients on the waiting list (black) in the U.S., 1991–2013**

In 1991, there were 6,953 donors, 15,757 organ transplants, and 23,198 patients on the waiting list. By 2013, there were 14,257 donors, 28,954 organ transplants, and 121,272 patients on the waiting list. (Data obtained from <http://optn.transplant.hrsa.gov>.)



**Figure 2. Longest reported survival times of pig organ and cell xenotransplantation in preclinical trials (pig-to-nonhuman primate models)**

Microencapsulated pancreatic islets = 804 days (with re-Tx), 250 days (without re-Tx) (Sun et al [35]) (wild-type [WT] pigs); Neuronal cells = >521 days (Badin et al [31]) (CTLA4-Ig transgenic pigs); pancreatic islets = 396 days (van der Windt et al [36]) (hCD46 pigs); cornea (full thickness) = >933 days (Choi et al [37]) (WT pigs); hepatocytes = 243 days (with re-Tx), 80 days (without re-Tx) (Nagata et al [38]) (WT pigs); heterotopic heart = >500 days (Mohiuddin et al [18]) (GTKO/hCD46/hTBM pigs); kidney = >240 days (Tector AJ, personal communication) (GTKO/hCD55 pigs); orthotopic heart = 57 days (McGregor et al [19]) (GTKO/hCD55 pigs); liver = 9 days (Kim K et al [28]) (hCD55 pigs); lung = 5 days (Cantu et al [29]) (vWF-deficient pigs). Figure modified from Ekser B et al. [15].

**Table 1**Major advantages of pig organ, tissue, or cell xenotransplantation<sup>\*</sup>

Pigs would be ethically acceptable sources of organs and cells to many of the world's population
Pigs are easy to breed and have large litters
Pig organs have similarities to human organs in respect of anatomy and physiology
Pigs could provide an unlimited supply of organs, tissues, and cells
The unlimited supply will allow transplantation procedures in 'borderline' candidates who might otherwise be declined
Organs will be available immediately and electively
The detrimental effects of brain death on donor organs will be avoided
When bred and housed under 'clean' conditions, pigs could provide exogenous infection-free organs, tissues, and cells
The 'cultural' barriers to deceased human donation present in some countries, e.g. Japan, will be obviated
Illegal organ trafficking and the use of organs from executed prisoners will be obviated
Organ donation by living donors, with its potential life-threatening complications, will be avoided

<sup>\*</sup> Modified from Cooper et al [34] and Ekser et al [15].

**Table 2**Comparison of kidney function between healthy humans and GTKO pigs<sup>\*</sup>

	Human	GTKO <sup>**</sup> Pig
Sodium (mmol/L)	136–146	144
Potassium (mmol/L)	3.5–5.0	5.3
Chloride (mmol/L)	95–110	103.0
Calcium (mg/dL)	8.4–10.2	10.8
Phosphorus (mg/dL)	2.5–4.5	8.8
CO <sub>2</sub> (mmol/L)	21–32	28.1
Urea (mg/dL)	5.0–20.0	12.8
Creatinine (mg/dL)	0.6–1.1	1.1

<sup>\*</sup> Adapted from Ekser et al. [26].

<sup>\*\*</sup> GTKO =  $\alpha$ 1,3-galactosyltransferase gene-knockout.

**Table 3**

Comparison of liver function in healthy humans and GTKO pigs\*

	Human	GTKO Pig
AST (IU/L)	<40	37.0
ALT (IU/L)	<40	42.0
ALP (IU/L)	38–126	272
LDH (IU/L)	<170	472
GGT (IU/L)	<40	74
Tot Bilirubin (mg/dL)	0.3–1.5	0.2
Dir Bilirubin (mg/dL)	0.1–0.4	0.1
Tot Protein (g/dL)	6.3–7.7	5.9
Albumin (g/dL)	3.4–5.0	3.4
Cholesterol (mg/dL)	<200	81
Triglyceride (mg/dL)	<150	31
Glucose (mg/dL)	70–99	89
PTT (sec)	22.7–35.6	34.1
PT (sec)	11.3–14.5	13.6
INR	0.8–1.2	1.1
D-dimer (micg/mL)	<0.45	0.20
Fibrinogen (mg/dL)	200–400	250
Coagulation Factors (U/mL)		
<i>Factor II</i>	0.7–1.3	1.12
<i>Factor V</i>	0.7–1.5	6.02
<i>Factor VII</i>	0.6–1.6	2.36
<i>Factor VIII</i>	0.6–1.5	6.06
<i>Factor IX</i>	0.6–1.5	4.18
<i>Factor X</i>	0.7–1.5	1.97
<i>Factor XI</i>	0.6–1.4	4.07
<i>Factor XII</i>	0.5–1.7	4.95
<i>Plasminogen (%)</i>	75–150	3
<i>Protein C (%)</i>	70–140	11
<i>Protein S (%)</i>	58–128	11
<i>Anti-thrombin III (%)</i>	80–120	71

AST= aspartate transaminase, ALT= alanine transaminase, ALP= alkaline phosphatase, LDH= lactate dehydrogenase, GGT= gamma glutamyltransferase, INR= international normalized ratio, PT= prothrombin time, PTT= partial thromboplastin time, WT= wild-type, GTKO=  $\alpha$ 1,3-galactosyltransferase gene knock-out.

\* Adapted from Ekser et al. [26] and Ekser et al. [25].

**Table 4**

Comparison of parameters of corneas between humans and pigs \*

		Human	Pig
<b>Diameter (mm)</b>			
<i>horizontally</i>		11.7	14.9
<i>vertically</i>		10.6	12.4
<b>Thickness (μm)</b>			
<i>center</i>		536	666
<i>periphery</i>		593	714
<b>Reactive power (diopter)</b>		43.0	40.4
<b>Tensile strength (MPa)</b>		3.81	3.70
<b>Stress-strain pattern<sup>(a)</sup></b>	<b>α</b>	42.8	39.3
	<b>β</b>	2.97	2.97
<b>Stress-relaxation pattern<sup>(b)</sup></b>	<b>P(x100)</b>	85.6	64.6
	<b>K(-)</b>	0.0165	0.0553
	<b>1000s</b>	32%	59%

<sup>(a)</sup> α is a scale factor. β represents the exponent of the nonlinear relationship between stress and strain

<sup>(b)</sup> P is the value of G (t) at the end of the stress-relaxation test. K is the slope of fitted G (t)-ln t line.

\* Adapted from Hara and Cooper [11].